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PCT/GB 2005 / 001333

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1. Your reference	MG//PB60825P
2. Patent application number *(The Patent Office will fill in his part)*	0408083.4 — 8 APR 2004
3. Full name, address and postcode of the or of each applicant *(underline all surnames)*	Glaxo Group Limited Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, Great Britain
Patents ADP number *(if you know it)*	473587003
If the applicant is a corporate body, give the country/state of its corporation.	United Kingdom
4. Title of the invention	Novel compounds
5. Name of your agent *(if you have one)*	Corporate Intellectual Property
"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	GlaxoSmithKline Corporate Intellectual Property (CN9 25.1) 980 Great West Road BRENTFORD Middlesex TW8 9GS
Patents ADP number *(if you know it)*	8072555006
6. Priority: Complete this section if you are declaring priority from one or more earlier patent applications, filed in the last 12 months	Country / Priority application number *(if you know it)* / Date of filing *(day / month / year)*
7. Divisionals: etc Complete this section only if this application is a divisional application or resulted from an entitlement dispute (see note f)	Number of earlier application / Date of filing *(day / month / year)*
8. Is a Patents Form 7/77 (Statement of inventorship and of right to grant of a patent) required in support of this request?	Yes

Answer YES if:

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
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Description	15
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Priority Documents

Translations of priority documents

Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*

Request for preliminary examination and search *(Patents Form 9/77)*

Request for substantive examination *(Patents Form 10/77)*

Any other documents *(please specify)*

11. **I/We request the grant of a patent on the basis of this application**

Signature(s)____________ **Date:** 8-Apr-04

M Gibson

12. Name and daytime telephone number of person to contact in the United Kingdom — M Gibson 01279 644841

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NOVEL COMPOUNDS

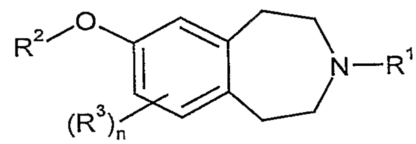
The present invention relates to novel benzazepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

JP 2001226269 and WO 00/23437 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives which are claimed to be useful in the treatment of obesity. DE 2207430, US 4,210,749 and FR 2171879 (Pennwalt Corp) and GB 1268243 (Wallace and Tiernan Inc) all describe a series of benzazepine derivatives which are claimed as being antagonists for narcotics (such as morphine or codeine) and also anti-histamines and anticholinergic agents. WO 02/14513 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives with GPR12 activity which are claimed to be useful in the treatment of attention deficit disorder, narcolepsy or anxiety. WO 02/02530 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as GPR14 antagonists which are claimed to be useful in the treatment of hypertension, atherosclerosis and cardiac infarction. WO 01/03680 (Isis Innovation Ltd) describe a series of benzazepine derivatives which are claimed as effective agents in the preparation of cells for transplantation in addition to the inhibition of diseases such as diabetes. WO 00/21951 (SmithKline Beecham plc) discloses a series of tetrahydrobenzazepine derivatives as modulators of dopamine D3 receptors which are claimed to be useful as antipsychotic agents. WO 01/87834 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as MCH antagonists which are claimed to be useful in the treatment of obesity. WO 02/15934 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as urotensin II receptor antagonists which are claimed to be useful in the treatment of neurodegenerative disorders. WO 04/018432 (Eli Lilly and Company) describe a series of substituted azepines as histamine H3 receptor antagonists for the treatment of obesity and other histamine H3 receptor related diseases.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel

H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents $-C_{2-7}$ alkyl or $-(CH_2)_m-C_{3-7}$ cycloalkyl;

R^2 represents -X-C_{3-8} cycloalkyl, -X-aryl, -X-heteroaryl, -X-C_{3-8} cycloalkyl-Y-C_{3-8} cycloalkyl, -X-C_{3-8} cycloalkyl-Y-aryl, -X-C_{3-8} cycloalkyl-Y-heteroaryl, -X-C_{3-8} cycloalkyl-Y-heterocyclyl, -X-aryl-Y-C_{3-8} cycloalkyl, -X-aryl-Y-aryl, -X-aryl-Y-heteroaryl, -X-aryl-Y-heterocyclyl, -X-heteroaryl-Y-C_{3-8} cycloalkyl, -X-heteroaryl-Y-aryl, -X-heteroaryl-Y-heteroaryl, -X-heteroaryl-Y-heterocyclyl, -X-heterocyclyl-Z-aryl, -X-heterocyclyl-Y-heteroaryl or –X-heterocyclyl-W-heterocyclyl, such that R^2 is linked to O via a carbon atom;

W represents C_{1-6} alkyl, CO, COC_{2-6} alkenyl, O or SO_2;

X represents a bond or C_{1-6} alkyl;

Y represents a bond, C_{1-6} alkyl, CO, COC_{2-6} alkenyl, O or SO_2;

Z represents a bond, CO, COC_{2-6} alkenyl, O or SO_2;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

m represents an integer from 1-3;

n is 0, 1 or 2;

wherein said alkyl groups of R^1 may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different and which are selected from the group consisting of halogen, cyano, =O, C_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^2 may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, =O, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamino, C_{1-6} alkylamido, $-R^4$, $-CO_2R^4$, $-COR^4$, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $-NR^5R^6$, $-C_{1-6}$ alkyl-NR^5R^6, $-C_{3-8}$ cycloalkyl-NR^5R^6, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5SO_2R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^4CONR^5R^6$ or $-SO_2NR^5R^6$ (wherein

R^4, R^5 and R^6 independently represent hydrogen, C_{1-6} alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl or $-NR^5R^6$ may represent a nitrogen containing heterocyclyl group, wherein said R^4, R^5 and R^6 groups may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl);
or solvates thereof.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-8} cycloalkyl fused to a phenyl ring, such as dihydroindenyl or tetrahydronaphthalenyl).

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl, azepanyl, imidazolidinyl, isothiazolidinyl, oxazolidinyl, pyrrolidinone and tetrahydro-oxazepinyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl, dihydroisoindole, dihydrobenzofuranyl, dihydrobenzothiopyranyl and dihydroisoquinolinyl.

The term "nitrogen containing heterocyclyl" is intended to represent any heterocyclyl group as defined above which contains a nitrogen atom.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring containing 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl and tetrahydropyranyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, furopyridinyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like.

Preferably, R^1 represents $-(CH_2)_m-C_{3-7}$ cycloalkyl (eg. $-CH_2$-cyclopropyl).

Preferably, m represents 1.

Preferably, R^2 represents -X-heteroaryl-Y-heterocyclyl (eg. –pyrazinyl-pyrrolidinyl) optionally substituted by an =O group, more preferably R^2 represents (-2-pyrazinyl-N-pyrrolidinyl) optionally substituted by an =O group (eg. –2-pyrazinyl-N-pyrrolidin-2-one).

Preferably, X represents a bond or $-CH_2-$, most preferably X represents a bond.

Preferably, Y represents a bond, CO, SO_2 or -CO-CH=CH- most preferably Y represents a bond or CO, especially a bond.

Preferably, n represents 0 or 1, more preferably 0.

When n represents 1, R^3 is preferably a halogen (eg. iodine) atom or a cyano group.

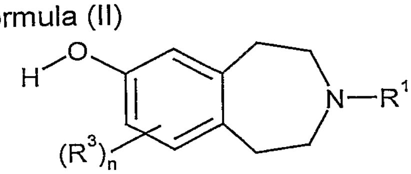
Preferred compounds according to the invention include example E1 as shown below, or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II)

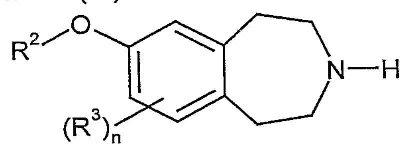


(II)

wherein R^1, R^3 and n are as defined above, with a compound of formula $R^{2'}$-L^1, wherein $R^{2'}$ is as defined above for R^2 or a group convertible thereto and L^1 represents a suitable

leaving group such as a halogen atom (eg. bromine or iodine) or an optionally activated hydroxyl group;

(b) reacting a compound of formula (III)



(III)

wherein R^2, R^3 and n are as defined above, with a compound of formula $R^{1'}$-L^2, wherein $R^{1'}$ is as defined above for R^1 or a group convertible thereto and L^2 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine or tosylate); or

(c) reacting a compound of formula (III) as defined above, with a ketone of formula $R^{1'}$=O, wherein $R^{1'}$ is as defined above for R^1 or a group convertible thereto; or

(d) deprotecting a compound of formula (I) which is protected; and

(e) interconversion to other compounds of formula (I).

When the leaving group L^1 is attached to an sp^3 hybridised carbon, for example, $R^{2'}$-L^1 is an alkyl halide, process (a) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a catalyst such as potassium iodide at an appropriate temperature such as reflux.

When the leaving group L^1 is attached to an sp^2 hybridised carbon, for example, $R^{2'}$-L^1 is an aryl halide, process (a) typically comprises the use of a copper(I) salt, such as copper (I) iodide, in the presence of a base such as sodium hydride, in an appropriate solvent such as pyridine, at an appropriate temperature such as reflux.

When the leaving group L^1 is attached to an activated sp^2 hybridised carbon for example, $R^{2'}$-L^1 is a heteroaryl halide such as a 2-chloropyridine or 2-chloropyrazine, process (a) typically comprises the use of a suitable base, such as sodium hydride in an appropriate solvent such as dimethylformamide or dimethyl sulfoxide, at an appropriate temperature. Alternatively, potassium tert-butoxide in tert-butanol at an appropriate temperature may also be employed.

When the leaving group L^1 is attached to an activated sp^2 hybridised carbon, for example $R^{2'}$-L^1 is an aryl halide such as 3,4-difluoro-benzonitrile, process (a) typically comprises the use of a suitable base, potassium carbonate, in a suitable solvent, such as dimethyl sulfoxide, at a suitable temperature.

When L^1 is a hydroxyl group attached to an sp^3 hybridised carbon, for example, $R^{2'}$-L^1 is an alcohol, process (a) typically comprises the use of a phosphine such as triphenylphosphine in a suitable solvent such as tetrahydrofuran, followed by addition of an azodicarboxylate such as diethylazodicarboxylate at a suitable temperature such as room temperature.

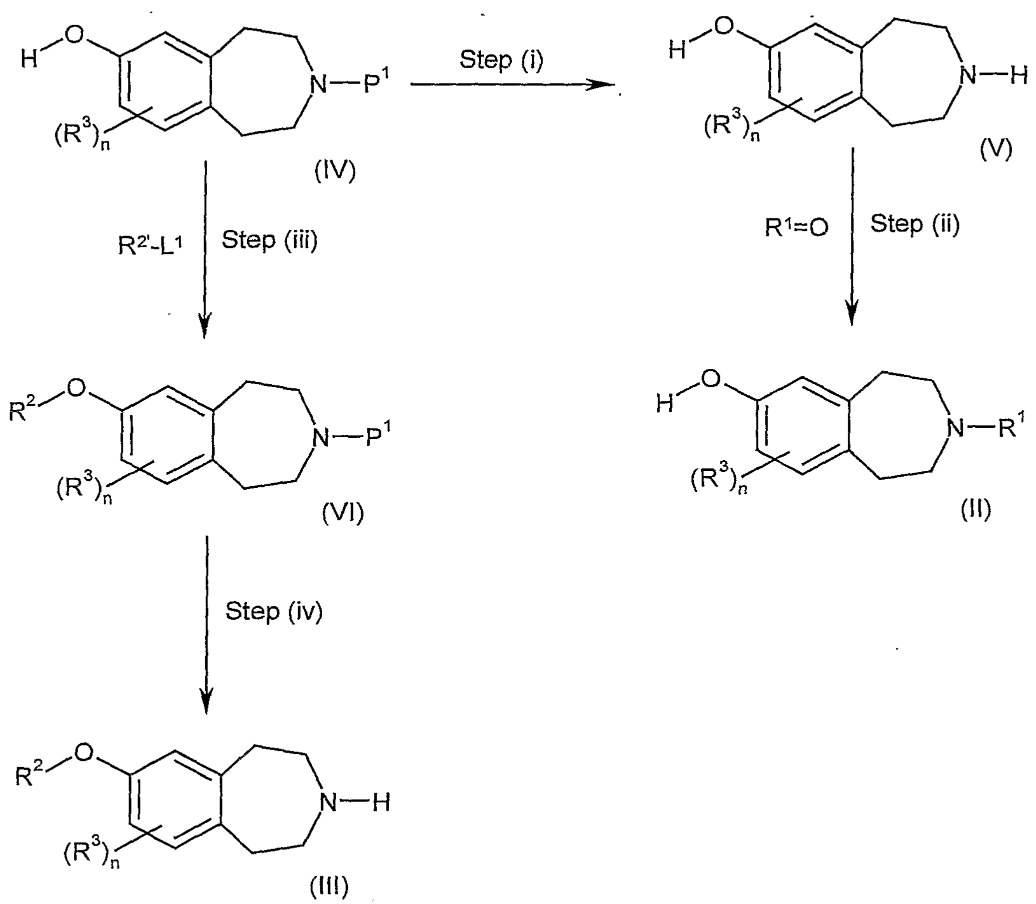
Process (b) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a catalyst such as potassium iodide at an appropriate temperature such as reflux.

Process (c) typically comprises the use of reductive conditions (such as treatment with a borohydride eg. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, in an appropriate solvent such as dichloromethane at a suitable temperature such as room temperature.

In process (d), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (e) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis, amide bond formation or transition metal mediated coupling reactions. Examples of transition metal mediated coupling reactions useful as interconversion procedures include the following: Palladium catalysed coupling reactions between organic electrophiles, such as aryl halides, and organometallic reagents, for example boronic acids (Suzuki cross-coupling reactions); Palladium catalysed amination and amidation reactions between organic electrophiles, such as aryl halides, and nucleophiles, such as amines and amides; Copper catalysed amidation reactions between organic electrophiles (such as aryl halides) and nucleophiles such as amides; and Copper mediated coupling reactions between phenols and boronic acids.

Compounds of formula (II) and (III) may be prepared in accordance with the following scheme



wherein R^1, R^2, $R^{2'}$, R^3, n and L^1 are as defined above and P^1 represents a suitable protecting group such as Boc.

Step (i) typically comprises a deprotection reaction, for example, when P^1 represents Boc the deprotection reaction comprises reaction of a compound of formula (IV) with an acid, for example hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

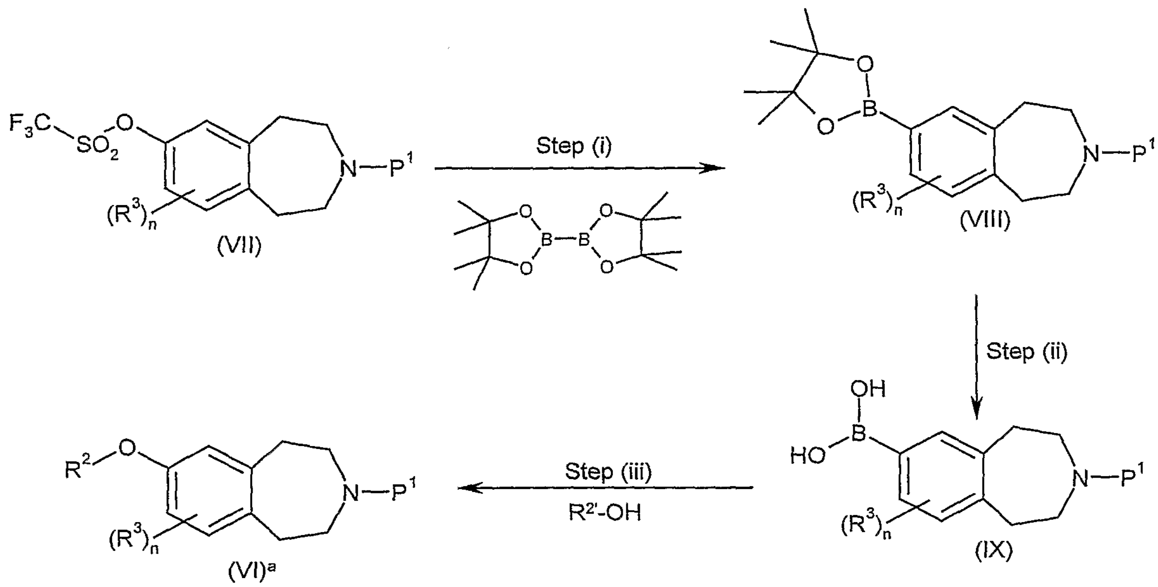
Step (ii) may be performed under reducing conditions in an analogous manner to that described for process (c).

Step (iii) may be performed in an analogous manner to that described for process (a).

Step (iv) typically comprises a deprotection reaction to provide a compound of formula (III) and can be performed as described in step (i).

Compounds of formula (VI) wherein R^2 represents -X-aryl, -X-heteroaryl, -X-aryl-Y-C_{3-8} cycloalkyl, -X-aryl-Y-aryl, -X-aryl-Y-heteroaryl, -X-aryl-Y-heterocyclyl, -X-heteroaryl-Y-C_{3-8}

cycloalkyl, -X-heteroaryl-Y-aryl, -X-heteroaryl-Y-heteroaryl or -X-heteroaryl-Y-heterocyclyl and X represents a bond may also be prepared in accordance with the following scheme



wherein R^2, $R^{2'}$, R^3 and n are as defined above and P^1 represents a suitable protecting group such as Boc.

Step (i) may be performed under palladium catalysed cross-coupling conditions, for example using bis(diphenylphosphino)ferrocenedichloropalladium (II) complex and 1,1'-bis(diphenylphosphino)ferrocene as the catalyst system, in combination with a suitable base, such as potassium acetate, in a suitable solvent, for example dioxane, at a suitable temperature, for example reflux.

Step (ii) may be performed under oxidising conditions, for example using sodium periodate in the presence of ammonium acetate, in a suitable solvent system, such as acetone and water, at a suitable temperature, for example room temperature.

Step (iii) may be performed in the presence of a copper salt, for example copper acetate, in combination with a suitable base, such as triethylamine, together with molecular sieves, in a suitable solvent, for example dichloromethane, at a suitable temperature, for example room temperature.

Compounds of formula (IV) may be prepared in an analogous manner to those described in Description 3 of WO 02/40471.

Compounds of formula (VII) may be prepared as outlined in Bioorg.Med.Chem.Lett.; 10; 22; 2000; 2553-2556.

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as

$5\text{-}HT_6$ antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

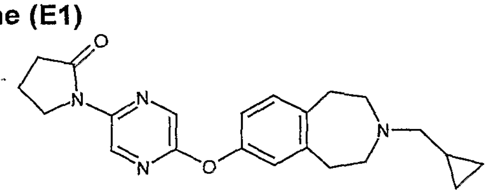
For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The

compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Examples illustrate the preparation of compounds of the invention.

Example 1
1-(5-{[3-(Cyclopropylmethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]oxy}-2-pyrazinyl)-2-pyrrolidinone (E1)



Step 1: 5-Chloro-2-pyrazinamine
Aminopyrazine (10g, 10.5mmole) was dissolved in dry dimethylformamide (60ml) and was treated with N-chlorosuccinimide (15.36g, 11.5mmole) under argon at 0°C. The mixture was stirred for 30 minutes and then allowed to warm to room temperature. The mixture was poured onto water and extracted with diethyl ether (x 5). The diethyl ether layers were combined and evaporated *in vacuo*. The resulting residue was purified by column chromatography (1:9 ethyl acetate:pentane) to afford the title compound (1.40g). ^{1}H NMR ($CDCl_3$) 8.02 (1H, s), 7.76 (1H, s), 4.61 (2H, s).

Step 2: 2,5-Dichloropyrazine
5-Chloro-2-pyrazinamine (product of E1, step 1) (2.41g, 18.6mmole) was dissolved in concentrated hydrochloric acid (24ml), cooled in an ice-acetone bath and treated with a

solution of sodium nitrite (2.63g, 38.1mmole) in water (18ml) dropwise over a period of 1 hour. The mixture was cooled in an ice-water bath and left to stir for 1 hour. The mixture was allowed to warm to room temperature over 1 hour, neutralised by addition of sodium hydroxide solution (2M) and extracted with dichloromethane (x 4). The dichloromethane layers were combined, dried under magnesium sulfate and evaporated *in vacuo*. The resulting residue was purified by column chromatography (1:9 ethyl acetate:pentane) to afford the title compound (0.33g). ^{1}H NMR ($CDCl_3$) 8.40 (2H, s).

Step 3: 1,1-Dimethylethyl 7-[(5-chloro-2-pyrazinyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate

1,1-Dimethylethyl 7-hydroxy-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (PCT Int. Appl. (2002), WO 02/40471) (182mg, 0.69mmole) was dissolved in dry dimethylformamide (3ml), cooled to 0°C and treated with sodium hydride (60% in mineral oil, 29mg, 0.72mmole). The mixture was allowed to warm to room temperature over 60 minutes. A solution of 2,5-dichloropyrazine (product of E1, step 2) (112mg, 0.76mmole) in dry dimethylformamide (1 ml) was added and the mixture stirred at room temperature for 2 hours. The mixture was diluted with water (10ml) and extracted with ethyl acetate (x 2). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography eluting with ethyl acetate/pentane (1:4) to afford the title compound (208mg). MS (ES+) m/e 376 $[M+H]^+$.

Step 4: 1,1-Dimethylethyl 7-{[5-(2-oxo-1-pyrrolidinyl)-2-pyrazinyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate

1,1-Dimethylethyl 7-[(5-chloro-2-pyrazinyl)oxy]-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E1, step 3) (208mg, 0.55mmole), pyrrolidinone (0.08ml, 1.1mmole), potassium carbonate (273mg, 1.98mmole), copper (I) iodide (32mg, 0.17mmole) and N,N-dimethylethylenediamine (0.02ml, 0.17mmole) were added together in dry dioxane (5ml) and heated in a microwave reactor at 150 °C for 3 hours. The mixture was diluted with water and extracted with ethyl acetate (x 3). The ethyl acetate layers were combined, dried under magnesium sulfate and evaporated *in vacuo*. The residue was purified by column chromatography eluting with ethyl acetate/pentane (1:1) to afford the title compound (126mg). MS (ES+) m/e 425 $[M+H]^+$.

Step 5: 1-[5-(2,3,4,5-Tetrahydro-1*H*-3-benzazepin-7-yloxy)-2-pyrazinyl]-2-pyrrolidinone

1,1-Dimethylethyl 7-{[5-(2-oxo-1-pyrrolidinyl)-2-pyrazinyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E1, step 4) (126mg, 0.30mmole) was dissolved in dry dichloromethane (2ml), treated with trifluoroacetic acid (2ml) and the resulting mixture was stirred at room temperature for 2 hours. The solvent was removed *in vacuo* and the residue dissolved in methanol and applied to a SCX column eluting with methanol and 2M ammonia/methanol. The basic fractions were combined and concentrated *in vacuo* to afford the title compound (88 mg). MS (ES+) m/e 325 $[M+H]^+$.

Step 6: 1-(5-{[3-(Cyclopropylmethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]oxy}-2-pyrazinyl)-2-pyrrolidinone

1-[5-(2,3,4,5-Tetrahydro-1*H*-3-benzazepin-7-yloxy)-2-pyrazinyl]-2-pyrrolidinone (product of E1, step 5) (28mg, 0.09mmole) was dissolved in dry dichloromethane (2ml), treated with cyclopropanecarboxaldehyde (0.01ml, 0.18mmole) and acetic acid (1 drop) and the resulting mixture stirred for 15 minutes. Sodium triacetoxyborohydride (38mg, 0.18mmole) was added and the mixture stirred for 18 hours. The mixture was diluted with methanol and applied to a SCX column eluting with methanol and 2M ammonia/methanol. The basic fractions were combined and concentrated *in vacuo* to afford the title compound (35 mg). MS (ES+) m/e 379 $[M+H]^+$.

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without

phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of buffer A2 containing 50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) (pH 7.40) supplemented with 10e-4M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), 1mM ethylenediamine tetra-acetic acid (EDTA), 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in 4 volumes of buffer A2 by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -70°C.

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 binding assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10μl of test compound (or 10μl of iodophenpropit (a known histamine H3 antagonist) at a final concentration of 10mM) diluted to the required concentration in 10% DMSO;

(b) 10μl ^{125}I 4-[3-(4-iodophenylmethoxy)propyl]-1H-imidazolium (iodoproxyfan) (Amersham; 1.85MBq/μl or 50μCi/ml; Specific Activity ~2000Ci/mmol) diluted to 200pM in assay buffer (50mM Tris(hydroxymethyl)aminomethane buffer (TRIS) pH 7.4, 0.5mM ethylenediamine tetra-acetic acid (EDTA)) to give 20pM final concentration; and

(c) 80μl bead/membrane mix prepared by suspending Scintillation Proximity Assay (SPA) bead type WGA-PVT at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay

buffer to give a final volume of 80µl which contains 7.5µg protein and 0.25mg bead per well – mixture was pre-mixed at room temperature for 60 minutes on a roller.
The plate is shaken for 5 minutes and then allowed to stand at room temperature for 3-4 hours prior to reading in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data was analysed using a 4-parameter logistic equation.

(II) Histamine H3 functional antagonist assay

For each compound being assayed, in a white walled clear bottom 96 well plate, is added:-

(a) 10µl of test compound (or 10µl of guanosine 5'- triphosphate (GTP) (Sigma) as non-specific binding control) diluted to required concentration in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH);

(b) 60µl bead/membrane/GDP mix prepared by suspending wheat germ agglutinin-polyvinyltoluene (WGA-PVT) scintillation proximity assay (SPA) beads at 100mg/ml in assay buffer followed by mixing with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer to give a final volume of 60µl which contains 10µg protein and 0.5mg bead per well – mixture is pre-mixed at 4°C for 30 minutes on a roller and just prior to addition to the plate, 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer) is added;

The plate is incubated at room temperature to equilibrate antagonist with receptor/beads by shaking for 30 minutes followed by addition of:

(c) 10µl histamine (Tocris) at a final concentration of 0.3µM; and

(d) 20µl guanosine 5' [γ35-S] thiotriphosphate, triethylamine salt (Amersham; radioactivity concentration = 37kBq/µl or 1mCi/ml; Specific Activity 1160Ci/mmol) diluted to 1.9nM in assay buffer to give 0.38nM final.

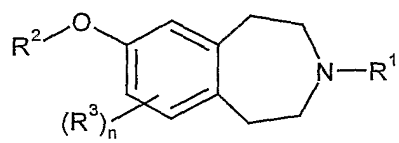
The plate is then incubated on a shaker at room temperature for 30 minutes followed by centrifugation for 5 minutes at 1500 rpm. The plate is read between 3 and 6 hours after completion of centrifuge run in a Wallac Microbeta counter on a 1 minute normalised tritium count protocol. Data is analysed using a 4-parameter logistic equation. Basal activity used as minimum i.e. histamine not added to well.

Results

The compound of Example E1 was tested in the histamine H3 functional antagonist assay and exhibited antagonism > 8.5 pK_b.

CLAIMS:

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents $-C_{2-7}$ alkyl or $-(CH_2)_m-C_{3-7}$ cycloalkyl;

R^2 represents -X-C_{3-8} cycloalkyl, -X-aryl, -X-heteroaryl, -X-C_{3-8} cycloalkyl-Y-C_{3-8} cycloalkyl, -X-C_{3-8} cycloalkyl-Y-aryl, -X-C_{3-8} cycloalkyl-Y-heteroaryl, -X-C_{3-8} cycloalkyl-Y-heterocyclyl, -X-aryl-Y-C_{3-8} cycloalkyl, -X-aryl-Y-aryl, -X-aryl-Y-heteroaryl, -X-aryl-Y-heterocyclyl, -X-heteroaryl-Y-C_{3-8} cycloalkyl, -X-heteroaryl-Y-aryl, -X-heteroaryl-Y-heteroaryl, -X-heteroaryl-Y-heterocyclyl, -X-heterocyclyl-Z-aryl, -X-heterocyclyl-Y-heteroaryl or –X-heterocyclyl-W-heterocyclyl, such that R^2 is linked to O via a carbon atom;

W represents C_{1-6} alkyl, CO, COC_{2-6} alkenyl, O or SO_2;

X represents a bond or C_{1-6} alkyl;

Y represents a bond, C_{1-6} alkyl, CO, COC_{2-6} alkenyl, O or SO_2;

Z represents a bond, CO, COC_{2-6} alkenyl, O or SO_2;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

m represents an integer from 1-3;

n is 0, 1 or 2;

wherein said alkyl groups of R^1 may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different and which are selected from the group consisting of halogen, cyano, =O, C_{1-6} alkyl, C_{1-6} alkoxy, haloC_{1-6} alkyl or haloC_{1-6} alkoxy;

wherein said cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^2 may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, =O, trifluoromethyl, trifluoromethoxy, fluoromethoxy, difluoromethoxy, C_{1-6} alkyl, pentafluoroethyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamino, C_{1-6} alkylamido, $-R^4$, $-CO_2R^4$, $-COR^4$, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $-NR^5R^6$, $-C_{1-6}$ alkyl-NR^5R^6, $-C_{3-8}$ cycloalkyl-NR^5R^6, $-CONR^5R^6$, $-NR^5COR^6$, $-NR^5SO_2R^6$, $-OCONR^5R^6$, $-NR^5CO_2R^6$, $-NR^4CONR^5R^6$ or $-SO_2NR^5R^6$ (wherein R^4, R^5 and R^6 independently represent hydrogen, C_{1-6} alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl or $-NR^5R^6$ may represent a nitrogen containing heterocyclyl group, wherein said R^4, R^5 and R^6 groups may be optionally substituted by one

or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl);
or solvates thereof.

2. A compound as defined in claim 1 which is a compound of formula E1 or a pharmaceutically acceptable salt thereof.

3. A pharmaceutical composition which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

4. A compound as defined in claim 1 or claim 2 for use in therapy.

5. A compound as defined in claim 1 or claim 2 for use in the treatment of neurological diseases.

6. Use of a compound as defined in claim 1 or claim 2 in the manufacture of a medicament for the treatment of neurological diseases.

7. A method of treatment of neurological diseases which comprises administering to a host in need thereof an effective amount of a compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition for use in the treatment of neurological diseases which comprises the compound of formula (I) as defined in claim 1 or claim 2 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.